**Supplement to:**

# Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Pharmacogenetics-guided Warfarin Dosing: 2016 Update

Julie A. Johnson[1], Kelly Caudle[2], Li Gong[3], Michelle Whirl-Carrillo[3], C. Michael Stein[4], Stuart A. Scott[5], Ming Ta Michael Lee[6], Brian F. Gage[7], Stephen E. Kimmel[8,9], Minoli A. Perera[10], Jeffrey L. Anderson[11], Munir Pirmohamed[12], Teri E. Klein[3], Nita A. Limdi[13], Larisa H. Cavallari[1], Mia Wadelius[14]

[1]Department of Pharmacotherapy and Translational Research, College of Pharmacy, and Center for Pharmacogenomics, University of Florida, Gainesville, Florida, USA
[2]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN
[3]Department of Genetics, Stanford University, Stanford, California, USA
[4]Division of Clinical Pharmacology Vanderbilt Medical School, Nashville, TN, USA
[5]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[6]Laboratory for International Alliance on Genomic Research, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; National Center for Genome Medicine; Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan; Genomic Medicine Institute Geisinger Health system, Danville, PA
[7]Department of Internal Medicine, Washington University in St. Louis, St. Louis, Missouri
[8]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
[9]Department of Medicine and Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
[10]Department of Medicine, University of Chicago, Chicago, IL, USA
[11]Intermountain Heart Institute, Intermountain Medical Center, and Department of Internal Medicine (Cardiology), University of Utah School of Medicine, Salt Lake City, Utah.
[12]Department of Molecular and Clinical Pharmacology; The Wolfson Centre for Personalised Medicine; Institute of Translational Medicine, University of Liverpool, Liverpool
[13]Department of Neurology and Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA
[14]Department of Medical Sciences, Clinical Pharmacology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden

Corresponding author: Julie A. Johnson, PharmD.; Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, Box 100484, Gainesville, FL 32610-0486; phone: 352-273-6309; fax: 352-273-6306; email: Johnson@cop.ufl.edu

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## GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for warfarin dosing is published in full on http://www.pharmgkb.org and https://cpicpgx.org/guidelines/. Relevant information will be reviewed periodically and updated guidelines published online.

## LITERATURE REVIEW

We searched the PubMed® database (1966 to 2016) for the following keywords: ((cytochrome P450 2C9 or CYP2C9) OR (VKORC1) OR (cytochrome P450 4F2 or CYP4F2) AND (warfarin) AND English [Language]). Using these search terms, 1221 publications were identified. In addition, studies annotated in PharmGKB (http://www.pharmgkb.org) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C9/VKORC1/CYP4F2* genotypes and metabolism of warfarin or warfarin-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded. Following application of these inclusion criteria, 183 publications were reviewed and included in the evidence tables (**Supplemental Tables S1- S7**).

The *CYP2C9/VKORC1/CYP4F2* frequency tables (https://www.pharmgkb.org/page/cyp2c9RefMaterials; https://www.pharmgkb.org/page/vkorc1RefMaterials; https://www.pharmgkb.org/page/cyp4f2RefMaterials) were made by searching the PubMed® database (1995 to 2016). The following criteria were used for *CYP2C9:* (CYP2C9 or 2C9 or cytochrome P4502C9) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity OR population) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2C9* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses). Similar search strategies were used for *VKORC1* and *CYP4F2* genes. Allele frequencies reported in phase 3 1000 Genomes were also included (http://browser.1000genomes.org/index.html) (1).

## DRUG: WARFARIN

### Background

Warfarin is administered as a racemic mixture of *R*- and *S*- stereoisomers. S-warfarin is 3-5 times more potent as a vitamin K antagonist than R-warfarin (2). The stereoisomers are extensively metabolized by different hepatic microsomal enzymes. S-warfarin is metabolized predominantly to 7- and 6- hydroxyl metabolites via CYP2C9 (**Figure 1**, **main manuscript**), whereas R-warfarin is mainly metabolized via CYP3A4 with involvement of CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18 and CYP2C19 (3-6).

Warfarin exerts its anticoagulant effect through inhibition of its molecular target Vitamin K epoxide reductase complex (VKORC1) (7). VKORC1 catalyzes the conversion of oxidized Vitamin K to reduced Vitamin K with the help of microsomal epoxide hydrolase (EPHX1). Warfarin blocks this reaction, which leads to decreased availability of the reduced Vitamin K that serves as a cofactor for gamma-glutamyl carboxylase (GGCX), and blocks the formation of functionally active clotting factors, leading to reduced coagulation (8-11).

**Dosing algorithms**

***IWPC warfarin pharmacogenetic dosing algorithm*** *(12)*

5.6044
- 0.2614 x Age in decades
+ 0.0087 x Height in cm
+ 0.0128 x Weight in kg
- 0.8677 x *VKORC1 A/G*
- 1.6974 x *VKORC1 A/A*
- 0.4854 x VKORC1 genotype unknown
- 0.5211 x *CYP2C9*1/*2*
- 0.9357 x *CYP2C9*1/*3*
- 1.0616 x *CYP2C9*2/*2*
- 1.9206 x *CYP2C9*2/*3*
- 2.3312 x *CYP2C9*3/*3*
- 0.2188 x *CYP2C9* genotype unknown
- 0.1092 x Asian race
- 0.2760 x Black or African American
- 0.1032 x Missing or Mixed race
+ 1.1816 x Enzyme inducer status
- 0.5503 x Amiodarone status
= Square root of weekly warfarin dose**

**The output of this algorithm must be squared to compute weekly dose in mg and divided by 7 to get the daily dose.

***Gage, et al.*** **(13)**

Estimated daily warfarin dose (mg/day) = Exp (0.9751 - 0.3238 x *VKOR_1639* + 0.4317 x BSA - 0.4008 x *CYP2C9**3 - 0.00745 x Age - 0.2066 x *CYP2C9**2 + 0.2029 x Target INR - 0.2538 x Amiodarone + 0.0922 x Smokes -0.0901 x AA_Race + 0.0664 x Prior_DVT_PE)
where exp is the exponential function, BSA is in $m^2$, the SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African American and 0 otherwise.

**EU-PACT** Loading Dose algorithm (14)

Loading dose (LD) over three days is calculated from the predicted maintenance dose (MD) as follows:

$$LD3=MD/ (1- \exp(-\kappa t))(1+ \exp(-\kappa t)+ \exp(-2\kappa t))$$

MD is the IWPC predicted weekly maintenance dose in mg divided by 7 days.

κ is the elimination rate constant for the CYP2C9 genotypes:

**1/*1* = 0.0189h-1
**1/*2* = 0.0158h-1
**1/*3* = 0.0132h-1
**2/*2* = 0.0130h-1

*2/*3 = 0.009h-1
*3/*3 = 0.0075h-1

$\tau$ is the warfarin dosing interval, use 24 (24h) for once daily dosing

The loading dose regimen is gradually reduced, i.e. Day 1 dose > Day 2 dose > Day 3 dose:
Loading on Day 1: (LD3-MD) x 1.5 + MD
Loading on Day 2: ((LD3-MD) x 1 + MD
Loading on Day 3: (LD3-MD) x 0.5 + MD

***Lenzini, et al. (15)***

Pharmacogenetic refinement algorithm: maintenance dose (mg/week) =
EXP (3.10894 − 0.00767 × age − 0.51611 × ln(INR) − 0.23032 × *VKORC1-1639 G*>A − 0.14745 × *CYP2C9*2* − 0.3077 × *CYP2C9*3* + 0.24597 × BSA + 0.26729 × Target INR −0.09644 × African origin − 0.2059 ×stroke − 0.11216 × diabetes − 0.1035 × amiodarone use − 0.19275 × fluvastatin use + 0.0169 × dose_2 + 0.02018 × dose_3 + 0.01065 × dose_4)
where VKORC1 -1639 G>A is entered as 0 for G/G, 1 for A/G and 2 for A/A, *CYP2C9* SNPs SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African origin and 0 otherwise.

**Other considerations**

***Clinical factors***. As highlighted in the dosing algorithms, clinical/demographic factors also significantly influence warfarin dose variability, the most significant of these being body size and age. An additional factor that is known to affect INR stability is patient non-adherence (16, 17). As with any drug, the patient should be counseled to ensure that there is an understanding of the importance of adherence to the prescribed warfarin regimen. In addition, genotype does not alter the importance of patient adherence.

***Drug interactions***. Drug interactions are common with warfarin, and significant interactions include both enzyme induction and enzyme inhibition. Smoking also causes enzyme induction. The dosing algorithms take into account some, but not all of the clinically important drug interactions with warfarin. Therefore, it is important to interpret the results of genetic testing in the context of other co-administered drugs.

***Other genes***. Variants in *CALU* and *GGCX* have been shown to affect warfarin dose and contribute to warfarin dose variations in some but not all populations. The effects of these variants are weaker than those of *CYP2C9* and/or *VKORC1*. Evidence linking these genes and other genes/variants to warfarin phenotype are presented in **Supplemental Table S6**.

Calumenin, encoded by gene *CALU*, is a Ca2+-binding protein retained in the endoplasmic reticulum. It binds to gamma—glutamyl carboxylase (GGCX) as an inhibitory chaperone to inhibit the vitamin K cycle and also affects the activity and warfarin sensitivity of VKORC1 (18). Genetic variations in *CALU* have been studied for their effect on warfarin dosing. One patient homozygous for the *CALU* rs2290228 variant allele was found with exceptionally high warfarin requirement (20mg/d) (19). However, this SNP and other *CALU* SNPs (rs11653, rs2307040, rs339054 and rs1006023) have not been shown to be significantly associated with warfarin dose in other studies (20). A new variant, rs339097 in *CALU*, has been identified that predicts higher warfarin dose in African Americans populations, with the G allele of rs339097 associated with a 14.5% higher therapeutic warfarin dose (21). Since variations in *VKORC1*, *CYP2C9* and *CYP4F2* genes only account for ~10% of the warfarin dose variations in African Americans, in contrast to ~35% in whites, identifying this additional SNP in *CALU* may help with prediction of warfarin dose, especially in the African American population. This variant is also more common in African Americans with minor allele frequencies of 11–14%, but only 0.2% in Caucasians. The correlation between rs339097 and higher warfarin dose requirement was confirmed in a study of 207 Egyptian patients (22).

Gamma-glutamyl carboxylase (GGCX) is a critical component of the vitamin K cycle (**Figure 1, main manuscript**) and catalyzes the post-translational carboxylation of vitamin K-dependent proteins (23). Many of these vitamin K-dependent proteins (clotting factors F2, F7, F9, F10 and protein C, S, Z) are involved in coagulation cascades. GGCX mediates the conversion of glutamate (Glu) residues to gamma carboxyl glutamate (Gla) on these proteins to make them functionally active with the reduced vitamin K serving as an essential cofactor. Rare non-synonymous mutations in *GGCX* have been linked with clotting disorders such as vitamin K-dependent clotting factor deficiency (VKCFD1, (24)) and Pseudoxanthoma Elasticum (PXE)-like disorder with multiple coagulation factor deficiency (25). Due to its pivotal role in the blood coagulations, genetic variations in the *GGCX* gene have been investigated for their impact on warfarin maintenance dose. One variant, rs11676382, was found to be associated with warfarin dose and explained 2% of total variance (26). This finding was confirmed in a large cohort (985 patients, mostly whites) where rs11676382 was shown to be a significant (p=0.03) predictor of residual dosing error and was associated with a 6.1% reduction in warfarin dose (95% CI: 0.6%-

11.4%) per G allele (11). Another variant in *GGCX*, rs12714145, was shown to be associated with warfarin dose in a Swedish cohort (201 patients, (27)), but failed to be replicated in subsequent studies (11, 20, 28, 29).

Genetic variation in folate homeostasis has also been shown to impact warfarin response. An association between lower warfarin dose requirements and the folate homeostasis gene, folypolyglutamate synthase gene (FPGS; rs7856096), has been reported in African Americans (30). However, this genetic variation does not appear to influence warfarin dose requirements in European-Americans and Egyptians (31).

***Alternative therapies to warfarin***. For over five decades coumarin anticoagulants, the most popular of which is warfarin, have been the only oral anticoagulants available world-wide. The approval of non-vitamin K anticoagulants, also known as novel oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban and edoxaban) provides an alternative to warfarin therapy in those with atrial fibrillation (32-36). While DOACs are not known to be influenced by genetic variability in *CYP2C9* and *VKORC1*, their pharmacokinetics or efficacy may be influenced by other genes (37). Advantages for NOACs include their rapid onset of anticoagulation, dosing simplicity for the clinician, and lack of need for monitoring. There are also disadvantages, which include twice daily dosing (dabigatran and apixaban), varying bioavailability (6 to over 80%), varying dependence on renal function for elimination (25 to 80%), the inability to monitor therapeutic effect, costs, limited clinical trial data for indications other than atrial fibrillation, contraindications for mechanic heart valves, and a 30-day shelf life once opened (dabigatran), among others (38, 39). As new oral anticoagulants gain market share, reliance on warfarin will decline. However, warfarin will continue to be widely utilized world-wide.

## LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Supplemental Tables S1-S7** is graded (40) on a scale of high, moderate, and weak, based upon the level of evidence:

**High:** Evidence includes consistent results from well-designed, well-conducted studies.

**Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
**Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations (**Main manuscript Table 2**).

## STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing gene, in vitro enzyme activity from tissues isolated from individuals of known genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline take into consideration the effects that *CYP2C9/VKORC1/CYP4F2* genetic variants may have on both clinical outcomes and warfarin pharmacokinetics.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (41):

**Strong** recommendation for the statement**:** "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."
**Moderate** recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

**Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

**SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2C9* TO WARFARIN PHENOTYPE**

| Type of experimental model | Major findings | References | Level of evidence* |
|---|---|---|---|
| **In vitro** | CYP2C9 is the primary enzyme catalyzing the metabolism and inactivation of S-warfarin. | Rettie, *et al.* (1992) (3)<br>Rettie, *et al*. (1994) (42)<br>Yamazaki, *et al.* (1998) (43) | High |
| **In vitro** | *CYP2C9*2* is associated with reduced catalytic activity. Substrate affinity is not affected substantially by the *2 haplotype, but the maximum rate of metabolism (Vmax) is reduced to approximately 50% of that for *CYP2C9*1* (wild-type). | Rettie, *et al.* (1994) (42)<br>Yamazaki, *et al.* (1998) (43)<br>Tang, *et al.* (2001) (44)<br>Lee, *et al.* (2002) (45)<br>Ho, *et al.* (2003) (46)<br>Kirchheiner, *et al.* (2005) (47) | High |
| **In vitro** | *CYP2C9*3* is associated with significantly reduced (nearly abolished for homozygotes) function of CYP2C9. | Lee, *et al.* (2002) (45)<br>Ho, *et al.* (2003) (46)<br>Kirchheiner, *et al.* (2005) (47) | High |
| **Clinical** | Individuals with *CYP2C9*2* and *CYP2C9*3* exhibit impaired metabolism of S-warfarin, leading to longer half-life of the drug. | Rettie, *et al*. (1994) (42)<br>Aithal, *et al.* (1999) (48)<br>Kirchheiner, *et al.* (2005) (47)<br>Daly, *et al.* (2006) (49)<br>Lindh, *et al.* (2009) (50) | High |

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| **Clinical** | Individuals with *CYP2C9*2* and *CYP2C9*3* have reduced warfarin maintenance dose. | Margaglione, *et al.* (2000) (51)<br>Taube, *et al.* (2000) (52)<br>Wadelius, *et al.* (2005) (27)<br>Samardzija, *et al.* (2008) (53)<br>Takeuchi, *et al.* (2009) (54)<br>Klein, *et al.* (2009) (12)<br>Pautas, *et al.* (2010) (28)<br>Cavallari, *et al.* (2011) (55)<br>Valentin, *et al.* (2012) (56)<br>Liang, *et al.* (2012) (57)<br>El Din, *et al.* (2012) (58)<br>Lee, *et al.* (2012) (59)<br>Pathare, *et al.* (2012) (60)<br>Liang, *et al.* (2013) (61)<br>Santos, *et al.* (2013) (62)<br>Ozer, *et al.* (2013) (63)<br>Limdi, *et al.* (2015) (64) | High |
| **Clinical** | *CYP2C9* variants with reduced activity (*CYP2C9*5, *6, *8,* and **11* alleles) have reduced warfarin maintenance dose. These variants most commonly occur in individuals of African ancestry. | Redman, *et al.* (2004) (65)<br>Tai, *et al.* (2005) (66)<br>Limdi, *et al.* (2007) (67)<br>Scott, *et al.* (2009) (68)<br>Cavallari, *et al.* (2010) (69)<br>Shahin, *et al.* (2011) (22)<br>Liu, *et al.* (2012) (70)<br>Cavallari, *et al.* (2013) (71)<br>Limdi, *et al.* (2015) (64) | High |
| **Clinical** | CYP2C rs12777823 variant is associated with reduced warfarin dose in African Americans, independent of *CYP2C9*2* and *CYP2C9*3*. | Perera, *et al.* (2013) (72)<br>Drozda, *et al.* (2015) (73)<br>Limdi, et al. (2015)(64) | High |
| **Clinical** | With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* have shorter time to therapeutic INR. | **Supports statement:**<br>Ruud, *et al.* (2008) (74)<br>Jorgensen, *et al.* (2009) (75)<br>Limdi, *et al.* (2009) (76) | Weak |

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| | | Pautas, *et al.* (2010) (28)<br>McMillin, *et al.* (2010) (77)<br>Ozer, *et al.* (2010) (78)<br>Zhong, *et al.* (2011) (79)<br><br>**Does not support statement:**<br>Higashi, *et al.* (2002) (80)<br>Limdi, *et al.* (2008) (81)<br>Schwarz, *et al.* (2008) (82)<br>Li, *et al.* (2009) (83)<br>Wadelius, *et al.* (2009) (84)<br>Lund, *et al.* (2012) (85)<br>Biss, *et al.* (2012) (86) | |
| **Clinical** | With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* require more time to achieve stable dose. | **Supports statement:**<br>Higashi, *et al.* (2002) (80)<br>Meckley, *et al.* (2008) (87)<br>Limdi, *et al.* (2008) (81)<br>Schwarz, *et al.* (2008) (82)<br>Caraco, *et al.* (2008) (88)<br>Kim, *et al.* (2009) (89)<br>Jorgensen, *et al.* (2009) (75)<br>Lund, *et al.* (2012) (85)<br><br>**Does not support statement:**<br>Lima, *et al.* (2008) (90)<br>Biss, *et al.* (2012) (86)<br>Finkelman, *et al.* (2015) (91) | High |
| **Clinical** | With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* have less time in INR therapeutic range (TTR) early in the course of therapy. | **Supports statement:**<br>Meckley, *et al.* (2008) (87)<br>Lima, *et al.* (2008) (90)<br>Limdi, *et al.* (2009) (76)<br>Wadelius, *et al.* (2009) (84)<br>Skov, *et al.* (2013) (92) | Moderate |

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| | | **Does not support statement:** Taube, *et al.* (2000) (52)<br>Moreau, *et al.* (2012) (93) | |
| **Clinical** | With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* are at increased risk of over-anticoagulation (INR>4). | **Supports statement:**<br>Higashi, *et al.* (2002) (80)<br>Peyvandi, *et al.* (2004) (94)<br>Voora, *et al.* (2005) (95)<br>Kealey, *et al.* (2007) (96)<br>Anderson, *et al.* (2007) (97)<br>Meckley, *et al.* (2008) (87)<br>Schwarz, *et al.* (2008) (82)<br>Lima, *et al.* (2008) (90)<br>Ruud, *et al.* (2008) (74)<br>Jorgensen, *et al.* (2009) (75)<br>Kim, *et al.* (2009) (89)<br>Limdi, *et al.* (2009) (76)<br>Wadelius, *et al.* (2009) (84)<br>Molden, *et al.* (2010) (98)<br>Pautas, *et al.* (2010) (28)<br>Moon, *et al.* (2011) (99)<br>Biss, *et al.* (2012) (86)<br>Ma, *et al.* (2012) (100)<br>Yang, *et al.* (2013) (101)<br>Gaikwad, *et al.* (2013) (102)<br>Kawai, *et al.* (2014) (103)<br>Mega, *et al.* (2015) (104)<br><br>**Does not support statement:**<br>Taube, *et al.* (2000) (52)<br>Limdi, *et al.* (2008) (81)<br>Li, *et al.* (2009) (83)<br>Lund, *et al.* (2012) (85)<br>Santos, *et al.* (2013) (62) | High |

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| | | Valentin, *et al.* (2014) (105) | |
| **Clinical** | With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* are at increased risk of bleeding. | **Supports statement:**<br>Ogg, *et al.* (1999) (106)<br>Margaglione, *et al.* (2000) (51)<br>Higashi, *et al.* (2002) (80)<br>Sanderson, *et al.* (2005) (107)<br>Samardzija, *et al.* (2008) (53)<br>Meckley, *et al.* (2008) (87)<br>Caraco, *et al.* (2008) (88)<br>Lima, *et al.* (2008) (90)<br>Ngow, *et al.* (2008) (108)<br>Limdi, *et al.* (2008) (109)<br>Wadelius, *et al.* (2009) (84)<br>Ma, *et al.* (2012) (100)<br>Yang, *et al.* (2013) (101)<br>Gaikwad, *et al.* (2013) (102)<br>Tomek, *et al.* (2013) (110)<br>Ucar, *et al.* (2013) (111)<br>Kawai, et al (2014)(103)<br>Valentin, *et al.* (2014) (105)<br>Mega, *et al.* (2015) (104)<br><br>**Does not support statement:**<br>Wadelius, *et al.* (2004) (112)<br>Limdi, *et al.* (2009) (76)<br>Esmerian, *et al.* (2011) (113)<br>Lund, *et al.* (2012) (85)<br>An, *et al.* (2014) (114)<br>Roth, *et al.* (2014) (115) | High |
| **Clinical** | *CYP2C9 *1/*14* and **1/*13* are associated with decreased warfarin dose in Korean patients | Kim, *et al.* (2009) (89)<br>Lee, *et al.* (2014) (116) | Moderate |

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| **Clinical** | *CYP2C9* rs7089580 variant is associated with higher warfarin dose in African Americans. It is also associated with higher S-warfarin clearance and CYP2C9 expression. | Perera, *et al.* (2011) (117)<br>Hernandez, *et al.* (2015) (118) | High |

*Rating scheme described in the Supplemental Material

**SUPPLEMENTAL TABLE S2. EVIDENCE LINKING *VKORC1* TO WARFARIN PHENOTYPE**

| Type of experimental model | Major findings | References | Level of evidence* |
|---|---|---|---|
| **In vitro** | *VKORC1-1639G>A* variant is associated with VKORC1 expression. | Rieder, *et al.* (2005) (119)<br>Yuan, *et al.* (2005) (120) | High |
| **Clinical** | VKORC1 is the protein target for warfarin. | Li, *et al.* (2004) (121)<br>Rost, *et al.* (2004) (7) | High |
| **Clinical** | *VKORC1-1639G>A* variant (and SNPs in high linkage disequilibrium with it) is associated with reduced warfarin maintenance dose. | Wadelius, *et al.* (2005) (27)<br>Rieder, *et al.* (2005) (119)<br>Yuan, *et al.* (2005) (120)<br>Schelleman, *et al.* (2007) (122)<br>Cooper, *et al.* (2008) (123)<br>Takeuchi, *et al.* (2009) (54)<br>Klein, *et al.* (2009) (12)<br>Limdi, *et al.* (2010) (124)<br>Pautas, *et al.* (2010) (28)<br>Suriapranata, *et al.* (2011) (125)<br>Liang, *et al.* (2012) (57)<br>El Din, *et al.* (2012) (58)<br>Lee, *et al.* (2012) (59)<br>Valentin, *et al.* (2012) (56)<br>Pathare, *et al.* (2012) (60)<br>Santos, *et al.* (2013) (62)<br>Ozer, *et al.* (2013) (63)<br>Limdi, *et al.* (2015) (64) | High |
| **Clinical** | With empiric warfarin dosing, individuals with *VKORC1-1639G>A* are likely to require shorter time to | Schelleman, *et al.* (2007) (122)<br>Meckley, *et al.* (2008) (87) | High |

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| | achieve first INR in therapeutic range, but have no difference in time to stable dose. | Limdi, *et al.* (2008) (81)<br>Schwarz, *et al.* (2008) (82)<br>Jorgensen, *et al.* (2009) (75)<br>Kim, *et al.* (2009) (89)<br>Limdi, *et al.* (2009) (76)<br>Li, *et al.* (2009) (83)<br>Wadelius, *et al.* (2009) (84)<br>Ozer, *et al.* (2010) (78)<br>McMillin, *et al.* (2010) (77)<br>Pautas, *et al.* (2010) (28)<br>Cavallari, *et al.* (2011) (55)<br>Zhong, *et al.* (2011) (79)<br>Lund, *et al.* (2012) (85)<br>Biss, *et al.* (2012) (86)<br>Finkelman, *et al.* (2015) (91) | |
| **Clinical** | With empiric warfarin dosing, individuals with *VKORC1-1639G>A* have less time in INR therapeutic range (TTR) early in the course of therapy. | **Supports statement:**<br>Wadelius, *et al.* (2009) (84)<br>Giansante, *et al.* (2012) (126)<br>Skov, *et al.* (2013) (92)<br><br>**Does not support statement:**<br>Meckley, *et al.* (2008) (87)<br>Moreau, *et al.* (2012) (93) | Moderate |
| **Clinical** | With empiric warfarin dosing, *VKORC1-1639G>A* is associated with increased risk of over-anticoagulation (INR>4) in Caucasians and Asians but not in African Americans. | **Supports statement:**<br>Anderson, *et al.* (2007) (97)<br>Schelleman, *et al.* (2007) (122)<br>Meckley, *et al.* (2008) (87)<br>Limdi, *et al.* (2008) (81)<br>Schwarz, *et al.* (2008) (82)<br>Kim, *et al.* (2009) (89)<br>Limdi, *et al.* (2009) (76)<br>Wadelius, *et al.* (2009) (84)<br>Molden, *et al.* (2010) (98) | High |

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| | | Pautas, *et al.* (2010) (28)<br>Moon, *et al.* (2011) (99)<br>Lund, *et al.* (2012) (85)<br>Biss, *et al.* (2012) (86)<br>Yang, *et al.* (2013) (101)<br>Gaikwad, *et al.* (2013) (102)<br><br>**Does not support statement:**<br>Ma, *et al.* (2012) (100) | |
| **Clinical** | With empiric warfarin dosing and INR monitoring, individuals with *VKORC1-1639G>A* are NOT at increased risk for major or minor bleeding event. | **Supports statement:**<br>Meckley, *et al.* (2008) (87)<br>Limdi, *et al.* (2008) (109)<br>Limdi, *et al.* (2009) (76)<br>Wadelius, *et al.* (2009) (84)<br>Esmerian, *et al.* (2011) (113)<br>Giansante, *et al.* (2012) (126)<br>Ma, *et al.* (2012) (100)<br>Yang, *et al.* (2013) (101)<br>Kawai, *et al.* (2014) (103)<br>An, *et al.* (2014) (114)<br>Roth, *et al.* (2014) (115)<br><br>**Does not support statement:**<br>Lund, *et al.* (2012) (85)<br>Gaikwad, *et al.* (2013) (102)<br>Tomek, *et al.* (2013) (110)<br>Valentin, *et al.* (2014) (105) | Moderate |
| **Clinical** | Multiple rare nonsynonymous SNPs in *VKORC1* (V29L (rs104894539), D36Y (rs61742245), V45A (rs104894540), R58G (rs104894541), V66M (rs72547529), R98W (rs72547528), L128R (rs104894542)) confer warfarin resistance. | Rost, *et al.* (2004) (7)<br>Harrington, *et al.* (2005) (127)<br>Bodin, *et al.* (2005) (128)<br>Harrington, *et al.* (2008) (129)<br>Scott, *et al.* (2008) (130)<br>Shahin, *et al.* (2011) (22) | High |

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| | Kurnik, *et al.* (2012) (131) |

*Rating scheme described in the Supplemental Material

**SUPPLEMENTAL TABLE S3. EVIDENCE LINKING CYP4F2 TO WARFARIN PHENOTYPE**

| Type of experimental model | Major findings | References | Level of evidence |
|---|---|---|---|
| **Clinical** | *CYP4F2* (rs2108622, V433M) variant allele is associated with a modest effect leading to higher warfarin dose in Europeans and Asians. | Stec, *et al.* (2007) (132)<br>Caldwell, *et al.* (2008) (133)<br>McDonald, *et al.* (2009) (134)<br>Takeuchi, *et al.* (2009) (54)<br>Singh, *et al.* (2010) (135)<br>Cen, *et al.* (2010) (136)<br>Sagreiya, *et al.* (2010) (137)<br>Wells, *et al.* (2010) (138)<br>Perini, *et al.* (2010) (139)<br>Lubitz, *et al.* (2010) (140)<br>Cavallari, *et al.* (2010) (69)<br>Pautas, *et al.* (2010) (28)<br>Shahin, *et al.* (2011) (22)<br>Kringen, *et al.* (2011) (141)<br>Liang, *et al.* (2012) (57)<br>Lee, *et al.* (2012) (59)<br>Pathare, *et al.* (2012) (60)<br>Bress, *et al.* (2012) (142)<br>Nakamura, *et al.* (2012) (143)<br>Liang, *et al.* (2012) (144)<br>Rusdiana, *et al.* (2013) (145)<br>Roth, *et al.* (2014) (115)<br>Wypasek, *et al.* (2014) (146)<br>Shendre, et al. (2016) (147) | Moderate |

**SUPPLEMENTAL TABLE S4. EVIDENCE COMPARING PHARMACOGENETICS WARFARIN DOSING ALGORITHMS TO STANDARD OF CARE DOSING[a] OR CLINICAL ALGORITHMS**

| Type of experimental model | Major findings | Reference | Level of evidence[b] |
|---|---|---|---|
| **Pharmacogenetics dosing algorithm vs standard of care dosing[a]** | | | |
| **Clinical** | More accurate prediction of dose | Anderson, *et al*. (2007) (148)<br>IWPC, *et al*. (2009) (149) | High |
| **Clinical** | Shorter time to stable dose with pharmacogenetics algorithm | Huang, *et al*. (2009) (150)<br>Borgman, *et al*. (2012) (151)<br>Wang, *et al*. (2012) (152)<br>Pirmohamed, *et al*. (2013) (14) | High |
| **Clinical** | Improved percent of time in therapeutic range (TTR) with pharmacogenetics algorithm | Huang *et al*. (2009) (150)<br>Borgman, *et al*. (2012) (151)<br>Anderson, *et al*. (2012) (153)<br>Pirmohamed, *et al*. (2013) (14)<br><br>**Does not support statement:**<br>Anderson, *et al*. (2007) (148) | High |
| **Clinical** | Reduced number of times with INR >4 with pharmacogenetics algorithm | Anderson, *et al*. (2012) (153)<br>Pirmohamed, *et al*. (2013) (14)<br><br>**Does not support statement:**<br>Anderson, *et al*. (2007) (148)<br>McMillin, et al. (2010) (77)<br>Borgman, *et al*. (2012) (151) | High |
| **Clinical** | Reduced number of times with INR <1.5 with pharmacogenetics algorithm | Anderson, *et al*. (2012) (153) | Moderate |

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|---|---|---|---|
| **Clinical** | Dosing with a pharmacogenetics algorithm does not reduce bleeding risk | McMillin, *et al.* (2010) (77)<br>Pirmohamed, *et al*. (2013) (14)<br><br>**Does not support statement:**<br>Anderson, *et al*. (2012) (153) | Weak |
| **Pharmacogenetics dosing algorithm including *CYP2C9*2, *3* and *VKORC1* vs clinical algorithm** | | | |
| **Clinical** | More accurate dose prediction in non-blacks | Lenzini, *et al*. (2008) (154)<br>IWPC, *et al*. (2009) (149)<br>Burmester, *et al*. (2011) (155)<br>Kimmel, et al. (2013) (156) | High |
| **Clinical** | Does not more accurately predict dose in blacks | Kimmel, et al. (2013) (156) | High |
| **Clinical** | Does not improve time to stable dose | Burmester, *et al*. (2011) (155)<br>Kimmel, *et al*. (2013) (156)<br>Jonas, *et al*. (2013) (157) | High |
| **Clinical** | Does not improve percent of time in therapeutic range (TTR) | Burmester, *et al*. (2011) (155)<br>Jonas, *et al*. (2013) (157)<br>Kimmel, *et al*. (2013) (156)<br><br>**Does not support statement:**<br>Lenzini, *et al*. (2008) (154) | High |
| **Clinical** | Does not reduce number of times with INR >4 | Burmester, *et al*. (2011) (155)<br>Kimmel, *et al*. (2013) (156)<br>Jonas, *et al*. (2013) (157) | High |
| **Clinical** | Does not reduce percentage of time below therapeutic range (INR<2) | Kimmel, *et al*. (2013) (156) | High |
| **Clinical** | Does not decrease bleeding risk | Lenzini, *et al*. (2008) (154)<br>Kimmel, *et al*. (2013) (156)<br>Jonas, *et al.* (2013) (157) | Weak |

[a]**Standard of care:** Standard of care for warfarin dosing is not same in all studies but is the standard of care relative to protocols incorporating genetic factors and/or clinical factors into the dosing consideration. It is usually a fixed initial dose (with our without a loading regimen), followed by dose modification according to results of the International Normalized Ratio (INR) or prothrombin time (PT) until a stable warfarin maintenance dose is achieved.

[b]Rating scheme described in the Supplemental Material

Note: Clinical utility studies not including *VKORC1* variant information are excluded from the analysis (Hillman 2005, Caraco 2008).

**SUPPLEMENTAL TABLE S5. PRIMARY PHARMACOGENETICS WARFARIN DOSING ALGORITHMS USED IN PROSPECTIVE CLINICAL TRIALS**

| Algorithm (ref) | Prospective clinical trial utilizing algorithm (ref) | Notes |
|---|---|---|
| IWPC (12) | COUMAGEN-II (153) | Modified version to accommodate different INR targets and smoking status |
| | EU-PACT (14) | Modified version used to calculate maintenance dose |
| Gage, *et al*. (13) | COAG (156) | Used for first 3 days of warfarin therapy |
| | GIFT | Not yet reported |
| Avery, *et al*. (158) | EU-PACT (14) | Modified version to account for *CYP2C9* allelic variants on the pharmacokinetics of warfarin was used to calculate loading dose for days of 1-3 therapy |
| Lenzini, *et al*. (15) | COAG (156) | Used to determine dose revision on day 4, 5, or both of therapy |
| | EU-PACT (14) | Modified version (by removing diabetes, African origin, stroke, and fluvastatin use) used to determine dose revision on days of 4-5 therapy based on the INR value on day 4. |

**SUPPLEMENTAL TABLE S6. ADDITIONAL FINDINGS WITH WEAK/MODERATE EVIDENCE LINKING OTHER GENES/VARIANTS TO WARFARIN PHENOTYPE (NOT PART OF RECOMMENDATION)**

| Type of experimental model | Major findings | References |
|---|---|---|
| **In vitro** | *CYP2C9*12* allele is associated decreased enzyme activity. | O'Brien, *et al.* (2013) (159) |
| **Clinical** | *CYP2C9 *1/*57* is associated with hyper sensitivity to coumarin anticoagulants with multiple bleeding episodes and supra-elevated INRs. | Nahar, *et al.* (2013) (160) |
| **Clinical** | *CYP2C9* rs17847036 GG genotype is associated with low dosage requirements in Indonesians | Suriapranata, *et al.* (2011) (125) |
| **Clinical** | *VKORC1-8191* (rs61162043) variant is associated with higher warfarin dose in African Americans. | Perera, *et al.* (2011) (117) |
| **Clinical** | The *VKORC1* rs17886199 A-allele is associated with lower warfarin dose in African Americans, independent of the *VKORC1 1173C>T* and *CYP2C9*2* and **3* variants. | Schelleman, *et al.* (2010) (161) |
| **Clinical** | *CYP4F2* rs2189784 (but not rs2108622) is associated with time-to-therapeutic INR. | Zhang, *et al.* (2009) (162) |
| **Clinical** | Variant rs339097 in *CALU* predicts higher warfarin dose in African Americans populations. | Voora, *et al.* (2010) (21)<br>Shahin, *et al.* (2011) (22) |

| | | |
|---|---|---|
| **Clinical** | Variant rs1043550 in *CALU* does not predict higher warfarin dose in Caucasians. | Glurich, *et al.* (2013) (163) |
| **Clinical** | rs11676382 in *GGCX* was shown to be a significant with a reduction in warfarin dose. | Rieder, *et al.* (2007) (26)<br>King, *et al.* (2010) (11)<br>Wypasek, *et al.* (2014) (146)<br>Sun, *et al.* (2015) (164) |
| **Clinical** | rs12714145/rs7568458 in *GGCX* are not associated with warfarin dose. | **Supports statement:**<br>Cha, *et al.* (2007) (29)<br>Wadelius, *et al.* (2007) (20)<br>Wadelius, *et al.* (2009) (84)<br>Pautas, *et al.* (2010) (28)<br>King, *et al.* (2010) (11)<br><br>**Does not support statement:**<br>Huang, *et al.* (2011) (165) |
| **Clinical** | Chinese patients carrying the *CYP2C19* rs3814637CC or GGCX rs699664AA genotype need higher warfarin doses. | Liang, *et al.* (2013) (61) |
| **Clinical** | Apolipoprotein E genotype is associated with duration of time to reach a stable warfarin dose in African-American patients. | Shahin, *et al.* (2011) (22)<br>Cavallari, *et al.* (2011) (166) |
| **Clinical** | *NQO1*2* (rs1800566) and *CYP4F2* V433M alleles are associated with higher therapeutic warfarin dose requirements in Hispanic-Americans, but not African-Americans. | Bress, *et al.* (2012) (142) |
| **Clinical** | *GATA4* regulates *CYP2C9* expression. *GATA4* SNPs (rs2645400 and rs4841588) are predictive of stable warfarin dose. | Jeong, *et al.* (2015) (167) |

**SUPPLEMENTAL TABLE S7. EVIDENCE LINKING *CYP2C9, VKORC1,* AND *CYP4F2* TO WARFARIN PHENOTYPE IN PEDIATRIC PATIENTS**

| Type of experimental model | Major findings | References | Level of evidence* |
|---|---|---|---|
| Clinical | Children with *CYP2C9*2* and *CYP2C9*3* have reduced warfarin maintenance dose. | **Supports statement:**<br>Nowak-Gottl, *et al.* (2010) (168)<br>Biss, *et al.* (2012) (86)<br>Moreau, *et al.* (2012) (93)<br>Shaw, *et al.* (2014) (169)<br>Hamberg, *et al.* (2014) (170)<br>Hawcutt, *et al.* (2014) (171)<br>Dilge Taskin, et al. (2016) (172)<br><br>**Does not support statement:**<br>Nguyen, *et al.* (2013) (173)<br>Kamal El-Din, *et al.* (2014) (174) | High |
| Clinical | With empiric warfarin dosing, children with *CYP2C9*2* and *CYP2C9*3* are at increased risk of over-anticoagulation. | Biss, *et al.* (2013) (175)<br>Shaw, *et al.* (2014) (169)<br>Hawcutt, *et al.* (2014) (171) | Moderate |
| Clinical | With empiric warfarin dosing, children with *CYP2C9*3* are at increased risk of bleeding. | Shaw, *et al.* (2014) (169) | Moderate |
| Clinical | *VKORC1-1639G>A* variant (and SNPs in high linkage disequilibrium with it) is associated with reduced warfarin maintenance dose in children. | **Supports statement:**<br>Nowak-Gottl, *et al.* (2010) (168)<br>Kato, *et al.* (2011) (176)<br>Biss, *et al.* (2012) (86)<br>Moreau, *et al.* (2012) (93)<br>Nguyen, *et al.* (2013) (173)<br>Hawcutt, *et al.* (2014) (171)<br>Shaw, *et al.* (2014) (169) | High |

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|---|---|---|---|
| | | Hamberg, *et al.* (2014) (170)<br>Wakamiya, et al (2016) (177)<br>Dilge Taskin, et al (2016) (172)<br><br>**Does not support statement:**<br>Hirai, *et al.* (2013) (178)<br>Kamal El-Din, *et al.* (2014) (174) | |
| Clinical | With empiric warfarin dosing, children with *VKORC1-1639G>A* are likely to require shorter time to achieve first INR in therapeutic range. | Shaw, *et al.* (2014) (169) | Moderate |
| Clinical | With empiric warfarin dosing, children with *VKORC1-1639G>A* have more time in INR therapeutic range (TTR). | Hawcutt, *et al.* (2014) (171) | Weak |
| Clinical | With empiric warfarin dosing, *VKORC1-1639G>A* is associated with increased risk of over-anticoagulation (INR > 4 or INR exceeding target range) in children. | Biss, *et al.* (2013) (175)<br>Shaw, *et al.* (2014) (169)<br>Hawcutt, *et al.* (2014) (171) (p=0.02, but not statistically significant after FDR adjustment) | High |
| Clinical | *CYP4F2* (rs2108622, V433M) variant allele is associated with a modest effect leading to higher warfarin dose in children. | **Supports statement:**<br>Hirai, *et al.* (2013) (178)<br><br>**Does not support statement:**<br>Biss, *et al.* (2012) (86)<br>Hamberg, *et al.* (2014) (170)<br>Wakamiya, et al. (2016) (177) | Weak |

*Rating scheme described in the Supplemental Material

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